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Is there an association between aspects of the metabolic syndrome and overactive bladder? A prospective cohort study in women with lower urinary tract symptoms

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ABSTRACT

Objective: The aim of our study was to determine whether there is a link between aspects of the metabolic syndrome (MetS) and overactive bladder (OAB) in women with lower urinary tract symptoms (LUTS).

Study design: A single-centre prospective study. We evaluated a cohort of consecutive women with LUTS attending a tertiary referral urodynamic clinic from October 2012 to January 2015. Obesity, diabetes, hypertension and dyslipidaemia were used as markers of MetS. OAB and detrusor overactivity (DO) were defined according to the International Urogynaecological Association/International Continence Society terminology.

Results: Eight hundred and forty women were enrolled. Three hundred and eight (36.6%) had normal weight, 260 (31%) were overweight and 272 (32.4%) obese. We identified 168 women (20%) with hypertension, 64 (7.6%) with diabetes mellitus, and 98 (11.7%) with dyslipidaemia. Seven hundred and four (83.8%) women were diagnosed symptomatically with OAB and 305 (36.3%) were diagnosed urodynamically with DO. Obesity ($p<0.001$) was the only independent predictor for OAB (OR 1.09, 95% CI 1.05-1.13) and DO (OR 1.06, 95% CI 1.03-1.08), respectively.

Conclusion: Our study demonstrates a correlation between obesity and OAB/DO in female patients. However, other components of MetS do not appear to be associated with either OAB and DO. Weight reduction should be strongly recommended in women with OAB.

Introduction

Overactive bladder (OAB) is a highly prevalent symptom complex that is estimated to affect 12.8% of women and 10.8% of men [1]. It is associated with a significant impairment of health-related quality of life and, subsequently, with a substantial economic burden [2]. The International Urogynaecological Association (IUGA) and International Continence Society (ICS) defined OAB as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [3]. OAB has usually been linked to the urodynamic observation of detrusor overactivity (DO), which is the occurrence of involuntary detrusor contractions during filling cystometry. However, DO is demonstrated in only 44% of women and 69% of men with OAB [4]. The underlying pathophysiological mechanism of OAB and DO is poorly understood. It is thought that, not only the detrusor muscle, but also urothelium, peripheral afferent terminals and pelvic blood vessels may play a role .

Since the last decade, authors have looked into a causal relationship between markers of the metabolic syndrome (MetS) and lower urinary tract symptoms (LUTS) [5]. MetS represents a cluster of cardiovascular disease (CVD) risk factors including obesity, dyslipidaemia, hypertension and glucose intolerance . Its rapidly increasing prevalence has recently been reported as 33% in the United States

[6]. However, comparisons between populations are challenging as numerous attempts have been made to define MetS and a conclusive agreement has not yet been received [7].

Several urological conditions, such as benign prostatic hyperplasia, nephrolithiasis, erectile dysfunction and OAB have been associated with different aspects of the MetS [8]. A number of mechanisms may be involved, mainly secondary to insulin-resistance and the subsequent production of chronic pelvic ischemia . However, while there is increasing evidence of a link between components of the MetS and OAB in men, limited data are available with regard to women [9,10]. Moreover, although it has been acknowledged that patients with DO experience more severe OAB symptoms [11], urodynamic findings have not been considered in the existing literature. A more comprehensive assessment of LUTS with urodynamics might give new insights.

The aims of this study were to determine whether there is a link between different aspects of the MetS and OAB/DO in women with LUTS.

Materials and methods

We prospectively studied a cohort of consecutive women with LUTS attending a urodynamic clinic in a tertiary referral urogynaecology department between October 2012 and January 2015. Formal ethical approval was obtained by the local Research Ethics Committees (12/SC/0012). We included women complaining of any LUTS [storage, urinary incontinence (UI), sensory, voiding and post-micturition symptoms]. Patients with at least one of the following characteristics were excluded: age < 18 years old, neurological condition affecting bladder function (such as dementia, stroke, multiple sclerosis, spinal cord injury and Parkinsons's disease), urine dipstick positive for nitrites and inability to fill out a questionnaire in the English language.

All women were asked to complete the validated King's Health Questionnaire [12] and a 3-day frequency-volume chart, including the Patient's Perception of Intensity of Urgency Scale (PPIUS) [13]. Antimuscarinic medications and mirabegron were stopped 7 days prior to attendance in the clinic,

where a detailed history was taken. Obesity, diabetes, hypertension and dyslipidaemia were considered as markers of MetS. Anthropometric measurements were calculated, including weight, height and body mass index (BMI) (weight [kg]/height [m]^2). Normal weight, overweight or obesity were defined as BMI 25 or less, between 26 and 30, or more than 30, respectively. Information regarding diabetes, hypertension and dyslipidaemia were collected from hospital records and patients were considered affected if already on relevant medical treatment.

Patients were asked to attend with a reasonably full bladder in order to obtain a uroflow study. A dipstick test to exclude urinary infection was performed. Examination findings were described using the pelvic organ prolapse quantification (POPQ) system during maximal Valsalva [14]. A Laborie Aquarius Triton machine was used to perform multichannel urodynamics by trained nurse specialists and trainees in urogynaecology in keeping with Good Urodynamic Practice [15].

Standard subtracted cystometry was performed with the patient in the supine position at a filling rate of 100 mL/min with physiological saline at room temperature. When DO did not occur, and following removal of the filling catheter, patients were instructed to perform provocative tasks (moving to the standing position, coughing, listening to running water and washing hands) and, finally, they were asked to void to completion.

Data were collected using a standardised proforma. Descriptive statistics were calculated for demographic information and clinical features. Several factors, including age, parity, menopausal status and markers for MetS (BMI, hypertension, diabetes mellitus and dyslipidaemia) were considered. These have been combined with both urinary symptoms and urodynamic diagnosis. Bivariate and multivariate logistic regression analyses were performed with associations presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). When statistical significance, defined with a p-value of <0.05, was achieved in univariate analysis, covariates were entered into the multivariate model. SPSS (V22, Chicago, IL, USA) was used for statistical analysis.

Results

Eight hundred and forty women were enrolled in the study. The mean age was 50.6 years (SD: 14.4) and the median parity was 2 (range 0-7). Four hundred and eighteen (49.8%) were postmenopausal. Three hundred and eight (36.6%) had normal weight, 260 (31%) were overweight and 272 (32.4%) obese. Table 1 shows the characteristics of the study group. We identified 168 women (20%) with hypertension, 64 (7.6%) with diabetes mellitus, and 98 (11.7%) with dyslipidaemia. Seven hundred and four (83.8%) women were diagnosed symptomatically with OAB, in particular 574 (68.3%) with "wet" OAB and 130 (15.4%) with "dry" OAB. Three hundred and five (36.3%) were diagnosed urodynamically with DO. Out of the 704 women with OAB, 282 (40%) were found to have DO. On the other hand, out of 305 patients with DO, 282 (92.4%) were reporting OAB symptoms. Figure 1 displays the study's flowchart.

Table 2 and Table 3 report associations with outcomes OAB and DO, respectively. With regard to OAB, age ($p=0.012$) and BMI ($p<0.001$) were found to be significant at univariate analyses, but only BMI (OR 1.09, 95% CI 1.05-1.13, $p<0.001$) maintained significance at multivariate analysis. When the outcome DO was considered, univariate analyses revealed significance for multiple factors, such as parity ($p<0.001$), BMI ($p<0.001$), hypertension ($p=0.003$) and diabetes mellitus ($p=0.004$). However, BMI (OR 1.06, 95% CI 1.03-1.08, $p<0.001$) was still the only independent predictor at multivariate analysis. No associations were found for menopausal status and dyslipidaemia with either outcome.

Discussion

In this study we evaluated associations between different aspects of the MetS with both OAB and DO in a cohort of women with LUTS. Unlike dyslipidaemia, hypertension and diabetes, obesity was a statistically significant risk factor for OAB and DO. To our knowledge, this is the first study considering DO, an objective diagnosis, alongside the symptom-based diagnosis of OAB.

Current evidence is conflicting but a link between MetS and OAB in female patients has been previously demonstrated [16-18]. Different definitions for MetS have been used, including the diagnostic criteria determined by the Ministry of Health, Labour and Welfare in Japan [16], the

National Cholesterol Education Program Adult Treatment Panel III criteria [17] and the International Diabetes Federation criteria [18]. Interestingly, international associations deem that MetS itself is still imprecisely defined [19] and, therefore, care should be taken before drawing definitive conclusions. Until much needed research is completed, clinicians should evaluate and treat all CVD risk factors, regardless the criteria for diagnosis of the MetS are met or not. Hence we focused on established aspects of MetS separately.

We found that obesity was the only independent risk factor for OAB (OR 1.09, 95% CI 1.05-1.13) and DO (OR 1.06, 95% CI 1.03-1.08). This is consistent with previously published studies [20-22]. Teleman et al. [20] evaluated 2682 women based on symptoms reported in the Bristol Female Lower Urinary Tract Symptoms questionnaire and BMI ≥ 30 (OR 1.5, 95% CI 1.1-2.1) resulted as an independent risk factor for OAB symptoms reported as "sometimes" or more often. 3962 females responded to a validated mailed survey [21] using the Epidemiology of Prolapse and Incontinence questionnaire. Women with BMI ≥ 30 were over twice as likely to experience OAB (OR 2.97, 95% CI 2.20-3.22). De Boer et al. [22] analysed 1397 women who filled out a validated Dutch translation of the Urinary Distress Inventory and, again, a BMI ≥ 30 resulted as an indipendent risk factor for OAB (OR 2.3, 95% CI 1.7-3.2). It is acknowledged that raised BMI can affect the detrusor muscle and chronically impair bladder function. However, these three studies show a stronger impact of BMI on OAB symptoms and the reason for this could lie in the analysed samples. In fact, while they evaluated low risk women from population registers, we considered patients attending a tertiary referral urogynaecology department. By definition, our sample is more likely to have complex medical and surgical histories, which might be able to affect the impact of BMI on OAB symptoms.

The role of the BMI is also supported by trials evaluating women's LUTS following bariatric surgery [23,24]. Of note, while most of the studies considered the effects on urinary incontinence, Palleschi et al. [24] assessed OAB severity in 120 morbidly obese patients following sleeve gastrectomy. At 6-month postoperatively, a significant reduction in the degree of bothersome OAB was noted.

Interestingly, Luke et al. [23] found that improvement in LUTS occurred early after bariatric procedures, suggesting an underlying mechanism other than just the weight loss. This could be represented by the insulin resistance, that can resolve early following bariatric surgery.

In our study, diabetes was not associated with OAB symptoms. When DO was considered as an outcome, diabetes showed a trend close to significance (OR 1.61, 95% CI 0.93-2.76, *p*=0.08). This conflicts with published literature. In a population-based study, Lawrence et al. [21] found that women with diabetes were 90% more likely to have OAB than women without diabetes (OR 1.90, 95% CI 1.46-2.49). In a large population-based study analysis including multiparous women of premenopausal age, a history of gestational diabetes was associated with double odds of OAB (OR 2.11, 95% CI 1.47-3.03) [25]. Interestingly, insulin resistance can adversely affect bladder nerves, smooth muscles and urothelium leading to DO in patients with diabetic cystopathy [26]. The variable diabetes was the least represented in our study, as 64 (7.6%) patients were affected. Therefore, in a larger sample, diabetes could reach significance and become a risk factor/predictor for DO.

We failed to demonstrate a link between the variables hypertension and dyslipidemia with either OAB and DO. This confirms the findings of Teleman et al. [20]. However, evidence in the literature is still limited. A population-based survey analysed 3599 women and, after adjustment for confounders, did not show a significant association between OAB and dyslipidaemia [27]. These variables were taken into account when a diagnosis of MetS was considered and a link with OAB was shown [16-18]. Further studies are required to shed light on these associations.

There is growing interest in a causative relationship between markers of MetS and LUTS. A common aetiology could underlie both conditions, but consensus is still lacking. Our findings support a “mechanical” mechanism. In fact, there is a correlation between increased BMI and intra-abdominal pressure, which can chronically stress the pelvic floor. Recently, studies have focused on the role of chronic pelvic ischemia and subsequent reduced blood flow to the bladder as causative factor for LUTS [28]. Animal models have been used to study ischaemia induced bladder dysfunction. It has been

argued that DO could derive from reactive oxygen species formed following ischaemia/reperfusion [29]. However, we cannot support this theory as there was no significant impact of dyslipidaemia, hypertension and diabetes with regard, not only to OAB, but also to DO.

Among the limitations of our study, we recognise that MetS was not defined using agreed criteria and the period of time from initial diagnosis was not considered. We acknowledge this may influence OAB symptoms. In addition, we investigated the role of different aspects of the MetS in a population of women presenting with LUTS in our tertiary referral centre. As a consequence, despite the considerable size of the study population, conditions such as diabetes mellitus and dyslipidaemia were little represented and our study might be underpowered for drawing definite conclusions, in particular with regard to the MetS complex. However, post-hoc analysis using the formula by Peduzzi et al. [30] [N = 10 k / p, where k equals the number of covariates (independent variables) and p the smallest of the proportions of negative or positive cases in the population] suggested that we enrolled an adequate number of women. A minimum sample size of 432 (10 x 7 / 0.162) and 192 (10 x 7 / 0.363) was required for either outcomes OAB and DO, respectively. A waist circumference was not measured and diagnoses were based upon hospital records. Thus, cases of dyslipidaemia might have been underdiagnosed. Moreover, factors associated with urgency, such as smoking or alcohol consumption, have not been considered. Whilst MetS components have an impact, the analysis of recognised confounding factors might provide clinicians with additional and more functional information. Furthermore, a history of stress UI was not included in our analysis. In fact, OAB symptoms might develop as a consequence of “defensive voiding”, leading women to increase the number of micturitions/day in order to reduce the amount of urine in the bladder and, thus, inconvenient episodes of UI.

In conclusion, our present study on a link between aspects of MetS and OAB in female patients confirms a correlation between obesity and OAB. This is also supported by significantly increased odds of DO at urodynamics in raised BMI patients. However, other components of MetS do not appear to

be associated with either OAB and DO. Hence OAB cannot be considered an aspect of the MetS in female patients. We consider that a “mechanical” pathophysiological mechanism, mainly increased chronic intra-abdominal pressure, might explain our findings. Since obesity is a modifiable factor, weight reduction should be encouraged in women with LUTS. The possible benefits could also enhance the effectiveness of concomitant treatments, such as bladder retraining and medical therapy. Future analyses might explore the therapeutic value of combining these interventions in patients with OAB. Inclusion of women with all aspects of the MetS should be considered to achieve a more comprehensive understanding of a link between MetS and OAB.

Table 1. Baseline characteristics of the study population

Table 2. Outcome: OAB

Table 3. Outcome: DO

CONFLICT OF INTEREST

Dr. Zacche reports non-financial support from Astellas, outside the submitted work.

Mr Giarenis reports personal fees and non-financial support from Astellas, outside the submitted work.

Mr Thiagamoorthy reports a grant from IUGA and non-financial support from Astellas, outside the submitted work.

Mr Robinson reports grants, personal fees and non-financial support from Astellas, personal fees from Allergan, grants and personal fees from Pfizer, personal fees from Ferring, outside the submitted work.

Dr. Cardozo reports grants, personal fees and non-financial support from Astellas, personal fees from Allergan, personal fees from Biomedical research (BMR), grants and personal fees from Pfizer, personal fees from Ferring and personal fees from Syner-Med, outside the submitted work.

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Figure 1. Flow diagram of the study

Figr-1

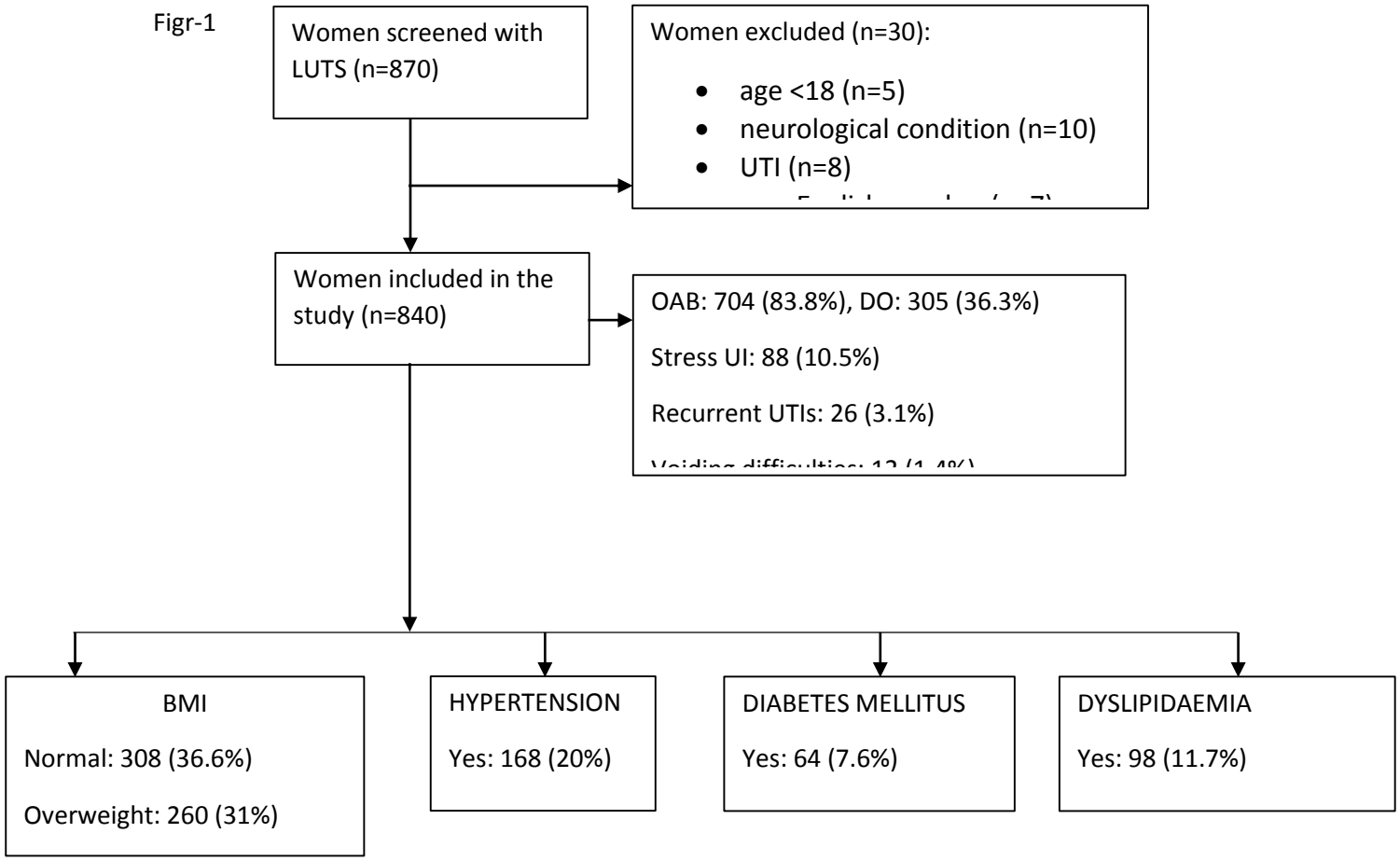

Figure 1. Flow diagram of the study

Table 1. Baseline characteristics of the study population (n=840)

Age, years, mean (SD)	50.6 (14.4)
Parity, median (range)	2 (0-7)
BMI, kg/m^2, n (%)	
<25	308 (36.6)
25-29.9	260 (31)
≥ 30	272 (32.4)
Menopausal, n(%)	418 (49.7)
Previous surgical procedures, n (%)	
Hysterectomy	186 (22.1)
Pelvic Floor Repair	89 (10.6)
Urinary Incontinence	85 (10.1)
King's Health Questionnaire, median (range)	
General Health Perception	25 (0-100)
Incontinence Impact	66 (0-100)
Role Limitations	50 (0-100)
Social Limitations	50 (0-100)
Physical Limitations	22 (0-100)
Personal Relationships	33 (0-100)
Emotions	44 (0-100)
Sleep/Energy	50 (0-100)
Severity/Coping Measures	50 (0-100)
Bladder diary, median (range)	
Daily urgency episodes	3 (0-14)
Daytime voids	8 (4-24)
Nighttime voids	1 (0-7)
Maximum functional capacity, mls	400 (90-1300)

Table 2 (Outcome: OAB)	**Univariate Analyses**		**Multivariate Analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	1.02 (1.00-1.02)	0.012*	1.00 (0.99-1.02)	0.24
Parity	1.06 (0.96-1.18)	0.23		
Menopause	1.19 (0.89-1.59)	0.23		
BMI	1.09 (1.05-1.13)	<0.001*	1.09 (1.05-1.13)	<0.001*
Hypertension	1.41 (0.88-2.23)	0.15		
Diabetes mellitus	1.74 (0.78-3.90)	0.17		
Dyslipidaemia	1.19 (0.66-2.12)	0.56		
* statistical significance				

Table 3 (Outcome: DO)	**Univariate Analyses**		**Multivariate Analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	1.01 (0.99-1.01)	0.23		
Parity	1.16 (1.07-1.25)	<0.001*	1.03 (0.93-1.15)	0.52
Menopause	0.93 (0.74-1.18)	0.54		
BMI	1.06 (1.04-1.09)	<0.001*	1.06 (1.03-1.08)	<0.001*
Hypertension	1.68 (1.19-2.36)	0.003*	1.27 (0.88-1.84)	0.20
Diabetes mellitus	2.12 (1.27-3.54)	0.004*	1.61 (0.93-2.76)	0.08
Dyslipidaemia	1.43 (0.94-2.20)	0.097		
*statistical significance				